Chapter

Hepatitis C: An Overview

Syed Manzoor Kadri and Marija Petkovic

Abstract

Hepatitis C virus (HCV) has infected approximatelly 130–170 milion individuals in the form of chronic liver infection and hepatocellular carcinoma. In the majority of patients with the increased risk for hepatocellular carcinoma the initial rearrangement is fibrosis. HCV is a bloodborne virus. The most common route of the infection are drug use, injections, unsafe health care performance, transfusion and sexual transmission. The incubation period ranges from 2 to 6 weeks in case of HCV. HCV infection is diagnosed in the process of detecting of anti-HCV antibodies and if positive, a nucleic acid test for HCV ribonucleic acid (RNA) is done. Currently, the most promising treatment agents are direct-acting antivirals (DAAs). They have shown limited viral resistance, long treatment duration and higher cost with no proven benefits in the prevention of graft reinfections in HCV individuals. In the light of the aforementioned, there is a need to a more dubious research in the quest for the effective therapeutic modalities.

Keywords: HCV, diagnosis, management, vaccine

1. Introduction

The word "hepatitis" is defined as the liver inflammation. In the majority of individuals it is due to genetic diseases, iatrogenic effect (certain medications), sexual intercourse, being born to a mother who has hepatitis C, transfusion, tattooing, illegal drug use or high alcohol intake. Prior to 1992, while the screening of the blood supplies started in the US, hepatitis C was most commonly spread through blood transfusions, organ transplants and haemodialysis treatment. Hepatitis C virus (HCV) has infected approximately 130–170 million individuals in the form of chronic liver infection and hepatocellular carcinoma [1].

In the majority of patients with an increased risk for hepatocellular carcinoma, the initial rearrangement is fibrosis. HCV is a bloodborne virus (**Figure 1**) [2].

Chronic hepatitis C (CHC) patients are at high risk to develop life-threatening complications, including cirrhosis in 20% of cases and hepatocellular carcinoma (HCC) at an incidence of 4–5% per year in cirrhotic patients [3].

Recommended HCV routine testing is based on the high-risk individuals such as risk the use of illegal drugs, clotting factors prior 1987, received blood/organs before 1992, chronic haemodialysis, liver disease, healthcare, emergency, healthcare workers after needlestick injuries in case of to HCV-positive blood, children born to HCV-positive women [4].

The routine HCV testing is not recommended in the healthcare setting, especially in the emergency and public safety professionals, pregnant individuals, in-home contacts of HCV-positive individuals etc.

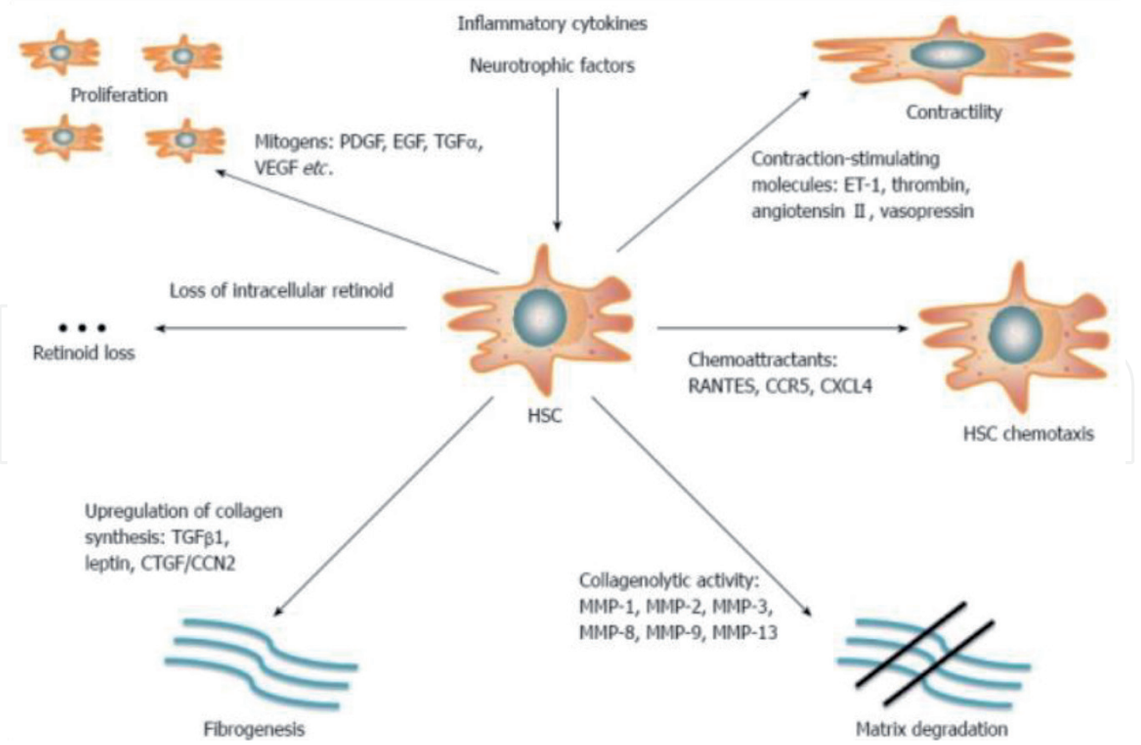

Figure 1.
Fibrogenesis. World J Gastroenterol. 2014. Doi: 10.3748/wjg.v20.i32.11033.

2. Epidemiology of hepatitis C virus

Hepatitis C is a disease with a worldwide burden, with the variable prevalence among major geographic areas. WHO estimates that about 170 million people or 3% of the world's population are infected with HCV [5].

The regions with high incidence are Eastern Mediterranean and European, with a prevalence of 2.3% and 1.5% respectively (**Figure 2**).

The estimated global prevalence of HCV infection is 3% which translates to over 180 million people worldwide [6].

High seroprevalence is noted in Asian and African countries. Egypt reported a seroprevalence of about 22% [7] and is highest in the world. A substantial regional difference exists in the distribution of HCV genotypes in the world. In Mexico, the estimated prevalence of HCV (2001–2002) was 1.2%. In the UK region, it has been estimated that nearly 200,000 adult individuals are HCV carriers. In Australia, the prevalence is estimated to be 2.3%. In Pakistan, HCV prevalence studies detected

WHO Region	Total Population (Millions)	Hepatitis C prevalence Rate %	Infected Population (Millions)	Number-of countries by WHO Region where data are not available
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	7
Europe	858	1.03	8.9	19
South-East Asia	1 500	2.15	32.3	3
Western Pacific	1 600	3.9	62.2	11
Total	5 811	3.1	169.7	57

Figure 2.
HCV prevalence.

that 751 out of 16,400 (4.57%) patients are +HCV Ab, while the rated are lower in Saudi Arabia and Yemen.

In Asia, the HCV prevalence among blood donors has been estimated lower than 0.49% (1995–2000.), with higher rates in Thailand (3.2–5.6%).

3. HCV characteristics

3.1 HCV genotype

Hepatitis C virus is an RNA viral microorganism. This virus belongs to the Flaviviridae family, genus Hepacivirus. It has one serotype, but minimum 6 major genotypes and over 80 subtypes [8].

The HCV virion is 55–65 nm in diameter. It consists of a 9.6 kbp positive-sense single-stranded RNA genome composed of a long open reading frame (ORF) flanked by untranslated regions (UTR's) at both the ends (**Figure 3**).

The genome of HCV is thought to encode at least 10 proteins, of which 3 are structural (core, envelope glycoproteins E1, E2) and 6 nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B).

HCV also expresses p7, a membrane-associated ion channel that may function during assembly or infection (**Figure 4**).

Two viral proteases are involved in the processing of HCV nonstructural proteins: NS2, a zinc-dependent metalloproteinase that cleaves between proteins NS2 and NS3, and NS3/4A, a serine protease that cleaves between the NS3-NS4A, NS4A-NS4B, NS4B-NS4B, NS4B-NS5A and NS5A-NS5B junctions [9].

3.2 Genetic variations of HCV

The HCV RNA sequences are highly heterogeneous. HCV is classified into 11 genotypes [1–11]. The several genotypes form further subtypes such as a, b, c etc.

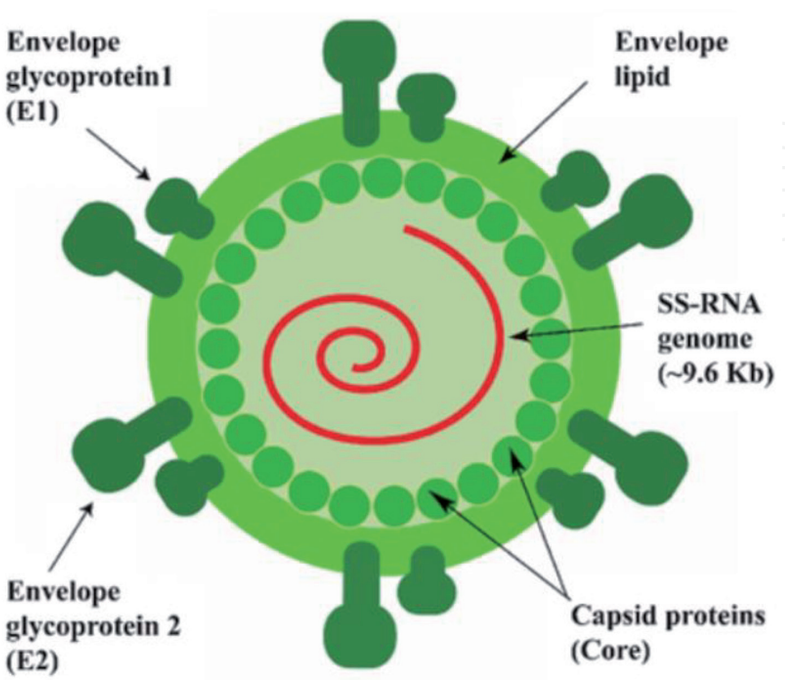

Figure 3.
Hepatitis C virus- an overview. 2018. Sagar Aryal

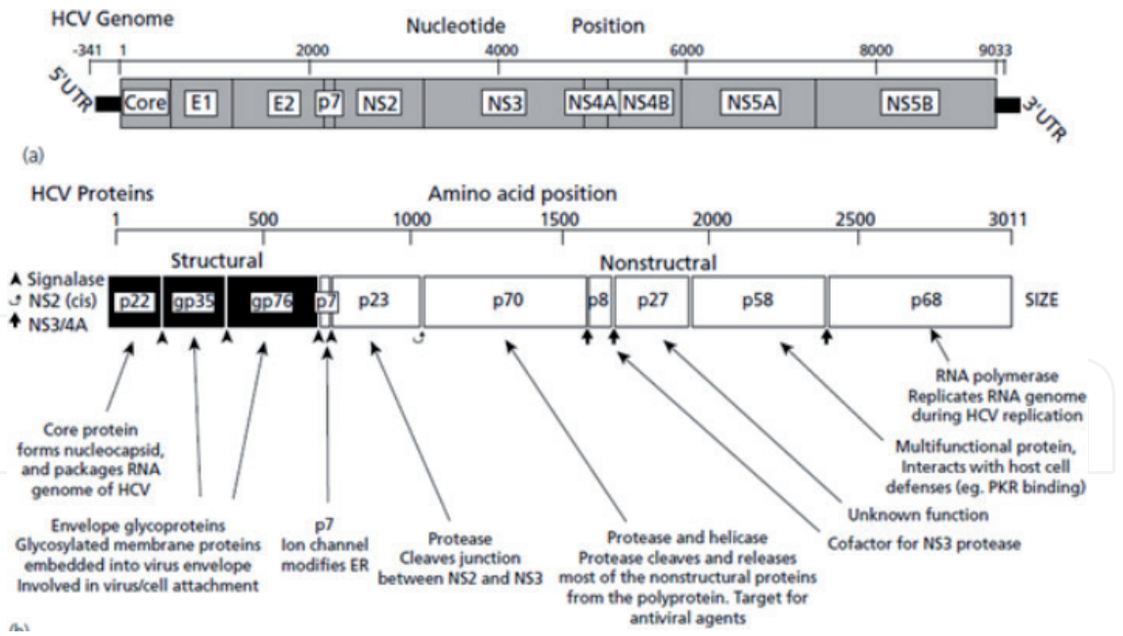

Figure 4.
HCV genome.

The classification is made according to the nucleotide sequence, variable infectivity and pathogenicity determining the progression rate of cirrhosis and hepatocellular carcinoma [11].

At this point, genotype 1 is the most prevalent (46%), then genotype 3,2 and 4 [12].

Core, a 191-amino acid polypeptide, may be involved in hepatocarcinogenesis and steatosis [13].

The importance of HCV genotype is highlighted in the case of the treatment response and the therapy duration.

The HCV genotype is characterised by the detection of antibodies against HCV genotype-specific epitopes with the application of competitive EIA.

HCV subtyping is of paramount importance in case of epidemics/pandemics, especially in case of epidemiological studies.

4. Pathogenesis of hepatitis C virus

The most common route of the infection is drug abuse, injections, unsafe health care performance, transfusion and sexual transmission.

The incubation period ranges from 2 to 6 weeks in case of HCV. HCV infection is diagnosed in the process of detecting anti-HCV antibodies and if possible, a nucleic acid test for HCV ribonucleic acid (RNA) is done [14].

The pathogenesis is characterised by HCV infected hepatocytes that may be destructed by HCV-specific CTL clones. The apoptotic mechanism is Fas ligand, TNF-α or perforin-based mechanism [15].

In the majority of cases, there is a slowly progressive asymptomatic hepatitis, with persistent viremia. The chronic form of the disease has a higher rate of progression to cirrhosis over a period of 20 years.

The exacerbation of the disease is characterised by elevated alanine aminotransferase activity. HCV –specific antibodies are detectable 7 to 31 weeks after the initial infection. Thus, the humoral immunity is highly variable and aimed towards the HCV core, envelope, NS3 and NS4 proteins [16].

The characteristic parenchyma impairments are the triad of steatosis, bile duct damage and the portal tracts [17].

Hepatic steatosis presents with large droplets of fat vacuoles in the cytoplasm of hepatocytes. In 20% of chronic hepatitis C cases, there is an eosinophilic deposit in the cytoplasm of periportal hepatocytes. Furthermore, the level of necroinflammation, fibrosis and cirrhosis depends on the serum alanine aminotransferase activity.

Predisposing factors such as viral co-infection (HBV etc.) and high alcohol consumption increase the risk of hepatic disease progression.

Chronic active hepatitis frequently leads to the onset of hepatocellular carcinoma (HCC) [18].

It has been postulated that in the case of HCV infection, the HCV-immune specific reaction is not adequate to control the viral replication due to high level of T-cell response.

The variety of polymorphism is associated with HCV prognostic diversity. The major cytokine involved in the molecular HCV infection pathway is the interleukin 28B [19].

5. Clinical manifestations of hepatitis C virus

5.1 Acute hepatitis

The incubation period for HCV is 7 weeks (2–26 weeks) after the initial exposure. The acute HCV infection presents with fever, fatigue, decreased appetite, nausea, vomiting, abdominal cramps, dark coloured faeces, grey facial skin, joint pain and jaundice [20].

5.2 Chronic hepatitis

In the patient with chronic hepatitis, the hepatic function is impaired. Additional symptoms are anorexia, nausea, right upper quadrant pain, dark coloured urine and pruritus. The serum level of ALT is either normal or elevated [21].

5.3 Hepatocellular carcinoma

The oncogenesis in the patients with chronic virus inflammation leads to the onset of necrosis, regeneration and cirrhosis [22].

6. Diagnostic assessment

In the majority of individuals, HCV viremia may be present in spite of normal serum ALT levels. Thus, the virological confirmation of HCV infection is more significant [23].

There is an HCV testing protocol such as to test the asymptomatic individuals: EIA for anti-HCV if negative (non-reactive) test no further if positive repeat testing or RIBA for anti-HCV. Recombinant immunoblot assays (RIBA) can be used to confirm the presence of anti-HCV antibodies.

The other possible testing pathway is to perform RT-PCR for HCV RNA if negative or if the positive result, proceed with medical evaluation [24].

In case RIBA test for anti-HCV is negative, [25] do not perform the further evaluation. In case the test is indeterminate (PCR negative, ALT normal or positive PCR, abnormal ALP continue with medial evaluation. In case both tests are positive, continue with the medical evaluation.

A serologic screening test is recommended to perform on individuals in the high-risk groups and nucleic acid tests are recommended to confirm the active HCV infections.

6.1 Laboratory diagnosis of HCV

Nowadays, HCV infection is detected by the use of serologic tests to detect HCV antibodies. Enzyme immunoassay (EIA) shows false negative in patients on haemodialysis. Immunodeficiency, and false-positive in an autoimmune disorder.

Recombinant immunoblot assay (RIBA) is a molecular assay that targets the amplification technique to detect HCV RNA.

A positive polymerase chain reaction (PCR) confirms HCV infection.

At present, the second-generation enzyme immunoassay (EIA-2) for antibodies to HCV (anti-HCV) is the most recommended diagnostic modality. If positive, the diagnosis may be confirmed by RIBA to detect antibodies to individual HCV antigens.

Anti-HCV is detected by the enzyme-linked immunosorbent assay (ELISA). In EIA, conserved antigens from the HCV core, NS3,NS4 and NS5 are used in the diagnostic laboratory.

EIAs to detect anti-HCV antibody are recommended for screening the HCV infections. It is not recommended in infants younger than 18 months due to the possible reactivity with the maternal antibody [26].

The serological window period is 40 days.

A screening test is the rapid, point-of-care test (POCTs) developed to detect anti-HCV antibodies with high sensitivity and specificity (OraQuick, OraSure Technologies). This test detects anti-HCV antibodies in different specimens (fingerstick, venipuncture whole blood, serum, plasma, oral fluid [27].

Confirmatory test such as recombinant immunoblot assay (RIBA) is used to confirm the presence of antibodies against each of the several HCV proteins is assessed as individual bands on a membrane strip [28].

HCV RNA level in the serum is probably the first detectable marker of acute HCV infection – a few weeks prior to the appearance of anti-HCV antibody by several weeks [29].

In the period prior and after the treatment, detection of HCV RNA is used to monitor the disease status. The level of HCV RNA is not in correlation with the hepatic disease stadium.

6.2 Molecular diagnosis of HCV

Qualitative reverse transcription-polymerase chain reaction (RT-PCR) assays for HCV RNA are simpler than quantitative tests and adequate for confirmation of the diagnosis of HCV [30].

Serum alanine aminotransferase level (ALT) is inexpensive, routine and noninvasive. It is great value for monitoring the disease activity.

6.3 Detection of viral RNA

Detection of HCV RNA by PCR and nucleic acid amplification tests (NAT) is performed, such as Transcript-Mediated Amplification (TMA).

Qualitative HCV RNA detection is defined as the use of conventional RT-PCR or transcription-mediated amplification (TMA) [31].

Quantitative NAT test is available in the form of quantitative RT-PCR (qRT-PCR) and branched deoxyribonucleic acid (bDNA) technology.

The indirect tests detect antibody induced by virus replication, IgM for recent infection, IgG for recent or past infection. The direct tests are virus isolation, detection of viral antigens and viral nucleic acids.

6.4 Detection of HCV core antigen

NATs test has higher specificity and sensitivity, but it is more time-consuming and in need of more sophisticated techniques. Currently, there are several generations of ELISA developed such as the one that uses the recombinant c100–3 epitope from the NS4 region, c22–3 and c33c from the HCV core and NS3 regions. The 4th generation of the anti-HCV assay is designed from the core, NS3, NS4A, NS4B and NS5A region.

6.5 Liver biopsy

The liver biopsy provides use of full information about the degree of fibrosis in HCV infected individuals [32].

The main benefit is to further manage the treatment protocol. The liver biopsy can assess the degree of inflammation, fibrosis, co-morbidities and therapeutic modalities [33].

Activity (necro-inflammation) severity and progress. May fluctuate with disease activity or therapeutic intervention [34].

Fibrosis implies possible progression to cirrhosis or in advanced disease defined as 'bridging fibrosis.'. To assess the degree of fibrosis, non-invasive tests (APRI or FIB4) are recommended.

7. Treatment

The initial HCV treatment was based on the application of interferon alfa, peginterferon and ribavirin [35].

The antiviral activity of interferon and peginterferon is based upon their ability to stimulate interferon-stimulated genes (ISGs) that have endogenous antiviral activities. Ribavirin is a nucleoside analogue that potentiates the effects of interferon against hepatitis by as yet undefined mechanisms [36].

Until 2020, the standard chronic HCV therapy was the combination of peginterferon and ribavirin given for 24 or 48 weeks. This combination led to sustained clearance of HCV and remission disease in 40–50% of patients. The response rate is higher in genotypes 2 and 3. [37].

In 2010, several HCV-specific protease inhibitors were approved for use: boceprevir, telaprevir and simeprevir specific to genotype 1 HCV. In 2013, sofosbuvir (HCV specific RNA polymerase inhibitor) was approved for the clinical treatment [38].

Other oral regimens become available in 2015, 2016 and 2017. They represented a combination of several HCV RNA polymerase regimens – nucleoside and non-nucleoside, HCV NS5A antagonists and the HCV protease inhibitors.

In individuals with cirrhosis, there is a higher risk of developing HCC and end-stage liver disease [39].

The combination of pegylated interferon plus ribavirin (PR) was the gold treatment standard (2000.). anti-HCV therapy requires weekly injections and is associated with numerous systemic side effects (flu-like symptoms, fatigue, etc.) [40].

The first approved in the USA according to FDA – boceprevir (Victrelis) and telaprevir (Incivek) for the treatment of chronic HCV genotype I infection [41].

Both drugs are classified as NS3/4A protease inhibitors, 24-28wk duration therapy, administered in combination with PR. FDA approved the different NS3/4A protease inhibitor named simeprevir (2013).

The HCV NS5B protein is an essential enzyme (RNA-dependant RNA polymerase) in HCV viral replication and has been a prime target in the search for antiviral therapies [42].

Adverse effects with interferon treatment: anaemia, neutropenia, rash, skin reactions, anorectal signs, elevated uric acid, bilirubin levels etc [43].

In the early 2000s, pegylated interferon plus ribavirin became the standard anti-HCV treatment. In 2014, boceprevir, telaprevir, simeprevir, sofosbuvir and Harvoni were approved by the FDA.

The highly significant antiviral treatment regimens are PEG-IFN + Ribavirin, – Telaprevir or boceprevir in genotype 1, -Sofosbuvir + Ribavirin ± PEG-IFN in genotypes 1,2,3 and 4, Simeprevir +PEG-IFN + Ribavirin in genotype 1 [44].

HCV has several genotypes detected. Therefore, an effective vaccine must be multivalent to have a beneficial treatment outcome.

There is no vaccine for Hepatitis C. The only way to prevent Hepatitis C is by avoiding behaviour that can spread the disease, especially injection drug use.

8. Prevention and control of hepatitis C

Screening of blood donors and screening for the presence of HCV prior to any transfusion of blood.

The use of sterile needles in case of medical and dental procedures, tattooing, or other percutaneous exposures [45].

Alcohol-intake decreased consumption or reduction will improve the overall health of an individual.

9. Conclusion

Currently, the most promising treatment agents are direct-acting antiviral (DAAs). They have shown limited viral resistance, long treatment duration and higher cost with no proven benefits in the prevention of graft reinfections in HCV individuals.

In light of the aforementioned, there is a need for more dubious research in the quest for the effective therapeutic modalities.

In summary, the diagnostic algorithm of Hepatitis C depends on the clinical context. In asymptomatic, low-risk subjects, who are found to be anti-HCV positive by EIA-2, the diagnosis of HCV infection needs to be confirmed, especially if the initial biochemical tests reveal normal ALT levels.

Author details

Syed Manzoor Kadri[1*] and Marija Petkovic[2]

1 Disease Control, Directorate of Health Services, Kashmir, India

2 University of Medicine, Belgrade, Serbia

*Address all correspondence to: kadrism@gmail.com

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